DEPARTMENT OF THE ARMY
DEFENSE AND VETERANS BRAIN INJURY CENTER
1335 EAST WEST HIGHWAY, SUITE 6-100
SILVER SPRING, MD 20910

INFORMATION PAPER

MCMR-DCV
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SUBJECT: CHRONIC TRAUMATIC ENCEPHALOPATHY

1.PURPOSE

Clarification of the neuropathological and clinical presentation of chronic traumatic encephalopathy (CTE) is critical for determining if there are clinical and pathological stages of progression, relating pathology to clinical symptoms, identifying risk factors, and developing interventions to prevent onset or spread of symptoms and pathology. The purpose of this IP is to summarize the available peer-reviewed scientific literature regarding the definition, epidemiology, risk factors, gross pathology, histology, molecular mechanisms, clinical manifestations, and prognosis for CTE to identify a list of specific gaps in our understanding of the disease that, if addressed, could inform the most appropriate prevention recommendations and allow clinicians to more effectively diagnose, manage, and treat CTE.

2. BACKGROUND

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease that is thought to be associated with repeated head trauma. The overwhelming majority of autopsy-confirmed cases have been seen in the setting of extended periods of time playing contact sports, such as boxing, American football and ice hockey. It appears to be a pathologically distinct entity from other neurodegenerative disease classifications, including frontotemporal dementia and Alzheimer's Disease (AD). At this time, diagnosis of CTE may only be determined by post-mortem neuropathological examination. Furthermore, there currently are no autopsy-validated clinical diagnostic criteria for CTE.

Appreciation of CTE as a distinct neurodegenerative disease has developed from case studies of athletes at risk for a high incidence of repetitive head trauma. A dementia syndrome occurring in former boxers, frequently accompanied by Parkinsonian and cerebellar motor signs, was first described by Martland in 1928 and initially called the "punch drunk" syndrome.(1) Cognitive symptoms include bradyphrenia (slowed thinking), confusion, and short-term memory impairment. The syndrome has subsequently been termed "dementia pugilistica," chronic encephalopathy of boxing, or, most recently, CTE. One early study of a sample of 224 retired boxers found that 17% had neurological symptoms consistent with the syndrome, and sub-syndromal cognitive impairment was apparent in 50%.(2) The onset of the clinical symptoms was insidious and occurred in middle age, with a mean of 16 years after discontinuation of boxing.(3) Disease progression was variable, and survival after the onset of neurologic or cognitive

impairment ranged from 7-35 years. Post-mortem cerebral histopathologic studies were not available for the boxers in that study, so it was not possible to correlate these clinical signs and symptoms with the pathologic changes associated with CTE.

3. INFORMATION

Etiology & Epidemiology: During the past 10-15 years there has been a renewed interest in CTE, prompted by the post-mortem identification of neuropathological features characteristic of CTE, such as cerebral atrophy, neurofibrillary tangles, and/or tau-immunoreactive neurites, in young or middle-aged American football players.(4,5) In a 2009 article, McKee and colleagues summarized available data from 48 cases where brain pathology was previously reported to be consistent with CTE, and presented clinical and pathological findings from 3 newly identified cases.(6) Subsequently, Stern and colleagues reported on 14 American football players diagnosed with CTE based on characteristic neuropathological findings.(7) In 2011, Gavett and colleagues published their findings suggesting the presence of CTE pathology in 12 football players.(8) Most recently, Goldstein and colleagues presented data from an additional series including four military veterans with a history of blast exposure and/or concussive injury, and four cases of young athletes that suffered repeat head trauma.(9) They contrasted the post-mortem findings in those eight cases with four cases without a history of blast exposure, concussive injury or neurologic disorders, and emphasized that none of the typical histopathologic features of CTE were present in those control cases.

The association between CTE and brain trauma is based on the fact that the known cases of CTE occurred in individuals with a history of head trauma, most of whom were contact-sports athletes, and especially those who had repetitive head trauma.(10) For example, 46 of the 51 cases summarized in the report by McKee and colleagues were athletes.(6) Of these, 39 were boxers, five were football players, one played soccer, and one was a professional wrestler. It has been estimated that football players at certain positions, such as the offensive line, may sustain as many as 1,444 head impacts in a single season.(11)

A dose-response relationship between the degree of CTE pathology and history of brain trauma has not been demonstrated. Moreover, not all of the individuals with a history of concussive or subconcussive head trauma who died and had detailed post-mortem examinations were found to have neuropathological features of CTE.(7,12) The risk of CTE or other neurodegenerative diseases may increase with repeated head trauma, but could also be associated with the severity of a single head trauma. An early study found that among boxers there appears to be a positive relationship between development of neurologic symptoms associated with CTE and the number of rounds fought, but not the number of knockouts.(2) While this study did not confirm CTE through

neuropathology examination, it suggests that the risk of developing a clinical syndrome that been associated with, but not necessarily specific to CTE, may be more related to the frequency of concussive or subconcussive blows to the head than to the severity of each blow. Additionally, Lehman, et al. reported that professional football players exposed to high velocity injuries (e.g., non-linemen) had as much as four times the rate of death from neurodegenerative diseases as the general population in the U.S.A, suggesting increased neurological risk with increased exposure to head trauma.(13) An association of CTE with gender, alcohol use, or exposure to chemical weapons such as organophosphates has not been studied.

It has been suggested that blast exposure may be a risk factor for developing CTE. However, this is only speculation based on mechanism and associated white matter injury documented in at least one study.(16) Recent postmortem studies of the brains of five veterans of the Iraq and Afghanistan conflicts illustrate the complexities of trying to establish the etiology of the disease.(9,17) These military cases comprise permutations of the combination of blast exposure (four cases), concussive injury (three or more of the cases), and post-traumatic stress disorder (three cases). In each of the cases with blast exposure, deposition of phosphorylated tau protein was similar to what was seen in other CTE cases without a history of blast exposure.(9,17) However, just as with studies of CTE in athletes, selection bias was inherent in the study of these veterans because they died prematurely. Their relatives agreed to the donation of their decedent's brains for neuropathological studies with the hope of better understanding the cause of death.

A determination of the true incidence and prevalence of CTE in the general population is not possible because there are no objective diagnostic criteria that can be used to reliably detect CTE prior to death, such as specific clinical criteria or imaging or molecular biomarkers. An imaging biomarker for AD has been described that uses an amyloid-binding radiotracer for positron emission tomography (PET) detection of β-amyloid.(14) But β-amyloid deposition is not a common feature of CTE in most studies, so this PET technique would not be expected to be sufficient for the pre-morbid identification of CTE. More recently investigators have used PET to explore whether brain tau deposits can be detected in 5 living retired National Football League (NFL) players (age 45-73) using 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) as a radioligand sensitive to Tau.(15) FDDNP signals were higher in players compared with age-matched controls in all subcortical regions studied, as well as the amygdala. However, autopsy confirmation of these findings is important before making any conclusions regarding pre-morbid identification of neurodegeneration in athletes involved in contact sports.

Clinical Manifestations: The clinical manifestations of CTE are limited to evidence obtained by interviewing relatives of deceased individuals, or retrospective reviews of medical records. There have not been any prospective studies linking CTE to specific clinical signs, symptoms or behaviors in living persons. It is thought that executive dysfunction is among the earliest symptoms of CTE.. Recent studies have tried to investigate this in living athletes; while these studies did not have neuropathology information to confirm CTE, the findings inform the type of clinical and behavioral manifestations that may develop later (after the fourth decade in life) for contact sport athletes. Specifically, in one study of 64 college and professional football players and age-matched controls with no history of contact sports who were administered the Behavior Rating Inventory of Executive Function, football players reported more-frequent problems with executive functioning, and symptoms were worse for those over 40 years old. (18) Another study investigated a common behavioral manifestation attributed to CTE - increased impulsiveness. In a study of a large group of active professional fighters, investigators found some associations of fight exposure with impulsiveness and reduction in volume of certain brain structures. (19) These findings suggest possible relationships that warrant further study to better understand the role of contact sports in developing clinical and behavioral manifestations later in life.

There are a number of possible mechanisms underlying late onset dementia following TBI, such as the presence of CTE, or the earlier clinical expression of age-related neurodegenerative diseases such as mild cognitive impairment (MCI) and AD. In a recent study of 513 retired NFL players data identified possible cognitive impairment in 35.1% of this relatively young sample.(20) Looking at neurocognitive data in a subsample of this group in comparison to a clinical sample of patients with a diagnosis of MCI due to AD revealed a similar profile of neurocognitive impairments. The investigators conclude the similar profiles may reflect that a common pathophysiology may underlie the cognitive impairment seen in both groups, and that this may be due to diminished cerebral reserve rather than CTE. These findings contrast somewhat with data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set that suggest an increased risk of late-life dementia following a TBI in early to mid-life.(21) This study found that only TBI with chronic deficit or dysfunction was associated with increased risk of dementia. Compared to patients with probable AD, patients with dementia associated with TBI were more likely to have symptoms of depression, agitation, irritability, and motor dysfunction. The authors conclude that their findings support that dementia in individuals with a history of TBI may be distinct from AD.

Most agree that the cognitive, emotional, and behavioral symptoms such as memory impairment, executive dysfunction, depression, irritability, and impulsivity that have been attributed to CTE are non-specific, and can be caused by numerous medical and psychiatric conditions. Even the symptom patterns typical of concussion/mild TBI, such as headache, dizziness, or sleep disorders, are non-specific. A literature survey of the frequency of concussion symptoms examined how common those symptoms were

in other disorders and in healthy control populations.(22) In some of the studies reviewed, the frequency of symptom endorsement in healthy individuals having no history of head injury actually exceeded the symptom endorsement rates in those with a history of concussion. The authors concluded that the heterogeneity of concussion symptoms, the absence of a unitary etiology of post-injury deficits, and the complex idiosyncratic time course of the appearance of these deficits are factors that make the diagnosis of concussion challenging. And despite claims that CTE occurs frequently in retired NFL players, recent studies of NFL retirees report that they have an all-cause mortality rate that is approximately half of the expected rate, and even lower suicide rates.(23) A systematic review of the medical literature of evidence for a relationship between CTE and suicide yielded two acceptable-quality case series that included autopsies from 17 unique cases, 5 of whom died by suicide.(24)Using the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) criteria, the quality of evidence for a relationship between CTE and suicide was rated as very low.

Pathology of CTE: The earliest known description of the gross pathologic manifestations of CTE are those described from studies of deceased boxers, and include reduced brain weight, cavum septum pelucidum, enlargement of the ventricles, and thinning of the corpus callosum, as well as presence of neurofibrillary tangles (NFTs).(25) Neurofibrillary tangles are a striking neuropathological feature of CTE that appear similar to NFTs found in AD, but with specific differences in the neuroanatomical localization.(26,27) Two large case series have demonstrated similar NFT neuropathology in the brains of former NFL players and other professional athletes with a history of repetitive mild TBI who either developed dementia and other clinical manifestations of CTE and died in middle age, or died (many via suicide) after displaying some of the cognitive features of CTE but prior to the development of dementia.(6, 12) CTE pathology has been reported in very young football players aged 17-26 years, and boxers in their 20s, but these subjects were not clinically evaluated before death to inform if they were symptomatic. (9,28)

Evidence that tau-related neurodegenerative processes are precipitated by TBI has been provided by human TBI epidemiology studies. Tau proteins regulate microtubule stability and are associated with NFTs. Patients with severe TBI exhibit transient elevations in cerebral spinal fluid (CSF) tau protein levels, which correlate with clinical outcomes at one year.(29) In the case of repetitive mild TBI-associated neurodegenerative dementias, considerable evidence points to abnormal neuronal processing of tau protein as an important contributor to neuropathology, such as the wide-spread deposition of cortical NFTs that are consistently observed in the brains of autopsied individuals with clinical symptoms prior to death. In addition to the effects of concussive impacts, the extent to which blast exposures contribute to the development of CTE is an important concern. Studies using a mouse blast model found that a single blast exposure induced phosphorylated tau pathology,

myelinated axonopathy, microvasculopathy, and chronic neuroinflammation and neurodegeneration.(9) Blast exposure in these mice also was associated with learning and memory deficits, but these cognitive deficits were not found when the head was immobilized during the blast and may therefore have been due to head acceleration.

Tau protein deposition is well known to be associated with neurodegenerative diseases and dementias, particularly frontotemporal dementia and AD. Neuropathological characteristics of phosphorylated tau (p-tau) and NFT formation have led to investigations of tau and related molecules that may be associated with neurodegeneration. Studies of more than 2,000 AD patients have consistently found a statistically significant increase of CSF tau levels in subjects with clinical AD,(30) though an age-associated increase of tau protein has also been reported in non-demented subjects and in patients with major head trauma, stroke, frontotemporal dementia, and Creutzfeldt-Jakob disease, suggesting that it is a general marker of neuronal damage.(31) In contrast, p-tau concentrations more specifically reflect NFT pathology and appear to be a sensitive marker of earlier neurodegenerative processes in AD. P-tau levels are elevated in patients with mild cognitive impairment (MCI) and correlate with progression from MCI to AD.(32,33)

Neurofilament low molecular mass protein (NF-L) as a potential indicator of axon damage also has been associated with the development of cognitive dysfunction following repeated TBI, though not directly with CTE. Zetterberg et al. measured CSF concentrations of NF-L in amateur boxers without known cognitive impairment three months after their last bout and found that the levels were higher than those in non-boxing control subjects.(34) A recent prospective study of Olympic amateur boxers revealed elevations of CSF levels for NF-L, total tau protein, glial fibrillary acidic protein (GFAP), and S100β at 1-6 days following a bout; CSF levels of NF-L and GFAP remained elevated following a 14-day rest period, suggesting ongoing neurologic injury in at least a subset of subjects.(35) Cerebral spinal fluid studies of neurodegenerative biomarkers such as tau, NF-L, GFAP, or S100β in patients with CTE have not yet been reported.

Trans-activator regulatory DNA-binding protein 43 (TDP-43) also has been associated with CTE and other neurodegenerative conditions.(36) TDP-43 immunoreactivity was present in distributed brain regions in 10 of 12 CTE cases.(37) Three of the cases of CTE with increased TDP-43 immunoreactivity also developed motor neuron disease with extensive spinal cord involvement. Recent findings of the McKee group suggest that more than 85% of CTE cases have abnormal accumulation of TDP-43 that are at least partially co-localized with phosphorylated tau protein.(38)

Beta amyloid (Aβ) deposition is evident at autopsy in a subset of reported cases of CTE. (6, 39) Altered proteolytic processing of amyloid precursor protein (APP) resulting in the production and aggregation of neurotoxic forms of Aβ peptide is widely believed to be central to the AD disease process, but it is not yet understood if Aβ plays a role in CTE. The mechanism for decreased CSF Aβ observed following TBI is unknown, but may reflect its increased aggregation and deposition into Aβ plaques in brain parenchyma. Because APP is transported to the axon terminal via microtubule-mediated mechanisms, APP is a marker of impaired axonal transport following TBI. It is important to emphasize that axonal damage with impaired axonal transport represents a mechanism for post-traumatic histopathology that does not necessarily implicate tau. However, tau phosphorylation abnormalities can destabilize microtubules and disrupt axonal transport. (40)

The apolipoprotein Eε4 (ApoEε4) genotype is well-known as a risk factor for early onset AD, as well as poor behavioral and functional outcomes following TBI.(41) Transgenic mice that overexpress the ApoEε4 allele have an increased deposition of Aβ following TBI.(6) The presence of at least one ApoEε4 allele was independently associated with lower performance on cognitive testing in professional football players,(42) and with increased severity of chronic neurologic deficits in boxers.(43) However, the association of the ApoEε4 genotype and CTE is unclear. Among 10 cases of neuropathologically confirmed CTE for which there was ApoE genotype information available, McKee and colleagues reported that only five had at least one ApoEε4 allele. (6) In their study of seven athletes with CTE and known ApoE genotype, Omalu et al found that only two had an ApoEε4 allele, and the other five were homozygous for ApoEε3.(12)

There is new imaging evidence of axonal injury associated with multiple head impacts in football players, based on data from diffusion tensor imaging. A single college football season of repetitive head impacts without clinically-evident concussion resulted in white matter changes associated with increased serum levels of ApoA1 and S100β autoantibodies, and correlated with multiple helmet impact measures.(44) These changes persisted for at least 6 months of no-contact rest. This lack of axonal recovery could potentially contribute to cumulative changes with subsequent repetitive head injuries. Diffuse white matter changes (e.g. axonal injury) can produce significant short and long term neurologic impairment by disconnecting brain networks. Investigators are beginning to focus on this damage by applying diffusion MRI techniques to large-scale intrinsic connectivity networks (ICNs). Damage to, and uncoupling of, ICNs have been found to produce predictable abnormalities in attention and cognition. (45)

4. SUMMARY

The purpose of this Information Paper was to review the current state of evidence for CTE. A thorough search of MEDLINE, CINAHL, EMBASE, Mosby's Index, PsycEXTRA, PsycINFO and Scopus has not

found any published epidemiological, cross-sectional or prospective studies relating to CTE.(46) Instead, the published studies are case reports or pathological case series, and it therefore is not possible to determine the causality or risk factors for CTE with any certainty. There is not sufficient evidence to prove that repeated concussion or subconcussive impacts cause CTE, and the extent to which age-related changes, psychiatric or mental health illness, alcohol/drug use or coexisting dementing illnesses contribute to the process of the development of CTE is largely unknown.

Significant gaps in our understanding of CTE remain:

- A clear definition of the neuropathological features of CTE is needed. A full range of case comparisons is needed to focus the definition of the neuropathological features of CTE as a distinct classification. The cases examined should include non-TBI, and comparisons across a range of known single and repeat TBI exposure levels. Comparisons should include cases with and without cognitive, behavioral, and neurologic manifestations common to CTE and known neurodegenerative diseases from which CTE must be distinguished. To the extent possible, comparisons should also include mental health conditions that share components of CTE symptoms.
- Neuropathology protocols for minimal sampling requirements for CTE in large autopsy-based studies are needed, including retrospective and prospective screening protocols that should be followed to facilitate identification of potential CTE cases in brain banks.
- Imaging (e.g. PET) and molecular biomarkers for CTE must be validated by autopsy confirmation.
- The typical phenotype – the cognitive, behavioral, psychiatric, and neurologic manifestations - of CTE need to be defined, and the progression of these manifestations delineated.
- A validated animal model of CTE is needed to better demonstrate the mechanism of injury relative to the neurodegenerative cascade and neuropathological features. The human neuropathological features of tau aggregation must be adequately modeled to contribute to mechanistic studies and screening of potential therapeutics.
- Traumatic risk factors for the development of CTE need to be much better defined, including the significance of the type of traumatic events (e.g. blast, blunt impact) number of events, the timing between events, and severity of individual events.
- Non-traumatic risk factors must be identified, such as history of depression, stress, alcohol and other drug use, age, gender, and genotype (e.g. ApoE alleles).

5. REFERENCES

1. Martland H. Punch drunk. JAMA. 1928; 91:1103 -7.

2. Roberts AH. Brain Damage in Boxers: A Study of the Prevalence of Traumatic Encephalopathy Among Ex-Professional Boxers. London: Pitman Medical and Scientific Publishing Co. Ltd.; 1969.
3. Critchley M. Medical aspects of boxing, particularly from a neurological standpoint. Br Med J 1957; 1(5015):357 - 62.
4. Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a national football league player. Neurosurgery. 2005 57(1)128-34.
5. Omalu BI, DeKosky ST, Hamilton RL, Minster RL, Kamboh MI, Shakir AM, Wecht CH. Chronic traumatic encephalopathy in a national football league player: part II. Neurosurgery. 2006 59(5):1086-92.
6. McKee AC et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. Journal of Neuropathology and Experimental Neurology. 2009; 68:709-35.
7. Stern RA et al. Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. PM R. 2011 Oct;3(10 Suppl 2):S460-7.
8. Gavett BE et al. Clinical appraisal of chronic traumatic encephalopathy: current perspectives and future directions. Curr Opin Neurol. 2011 Dec;24(6):525-31.
9. Goldstein LE et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Science Translational Medicine. 2012; 4:134ra60.
10. Erlanger DM, et al. Neuropsychology of sports-related head injury: Dementia Pugilistica to Post Concussion Syndrome. Clin Neuropsychol. 1999; 13:193-209.
11. Crisco JJ, Fiore R, Beckwith JG, Chu JJ, Brolinson PG, Duma S, McAllister TW, Duhaime AC, Greenwald RM. Frequency and Location of Head Impact Exposures in Individual Collegiate Football Players. J Athl Train. 2010 Nov-Dec; 45(6): 549–559.
12. Omalu B et al. Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. Neurosurgery. 2011; 69:173-83.
13. Lehman EJ et al. Neurodegenerative causes of death among retired National Football League players. Neurology. 2012 Sept [Epub ahead of print]
14. Price JC, Klunk WE, Lopresti BJ, Lu X, Hoge JA, Ziolko SK, Holt DP, Meltzer, CC, DeKosky ST, Mathis CA. Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. J Cereb Blood Flow Metab. 2005 Nov;25(11):1528-47.
15. Small, G. W., Kepe, V., Siddarth, P., Ercoli, L. M., Merrill, D. A., Donoghue, N., Barrio, J. R. (2013). PET scanning of brain tau in retired national football league players: preliminary findings. The American Journal of Geriatric Psychiatry, 21(2), 138-44.
16. Warden D. Military TBI during the Iraq and Afghanistan wars. J Head Trauma Rehabil. 2006 Sep-Oct;21(5):398-402.

17. Omalu B, et al. Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. Neurosurgical focus. 2011; 31:E3. .(Seichepine, D. R.,
18. Stamm, J. M., Daneshvar, D. H., Riley, D. O., Baugh, C. M., Gavett, B. E., … Stern, R. A. (2013). Profile of self-reported problems with executive functioning in college and professional football players. Journal of Neurotrauma, 30(14), 1299-304.
19. Banks, S. J., Mayer, B., Obuchowski, N., Shin, W., Lowe, M., Phillips, M., … Bernick, C. (2014). Impulsiveness in professional fighters. The Journal of Neuropsychiatry and Clinical Neurosciences, 26(1), 44-50.
20. Randolph, C., Karantzoulis, S., & Guskiewicz, K. (2013). Prevalence and characterization of mild cognitive impairment in retired national football league players. Journal of the International Neuropsychological Society, 19(8), 873-80.
21. Sayed, N., Culver, C., Dams-O'Connor, K., Hammond, F., & Diaz-Arrastia, R. (2013). Clinical phenotype of dementia after traumatic brain injury. Journal of Neurotrauma, 30(13), 1117-22.
22. Rapp PE, Curley KC. Is a diagnosis of "mild traumatic brain injury" a category mistake? J Trauma Acute Care Surg. 2012 Aug;73(2 Suppl 1):S13-23.
23. Randolph, C. (2014). Is chronic traumatic encephalopathy a real disease? Current Sports Medicine Reports, 13(1), 33-7.
24. Wortzel, H. S., Shura, R. D., & Brenner, L. A. (2013). Chronic traumatic encephalopathy and suicide: a systematic review. BioMed Research International, 2013, 424280.
25. Corsellis JA, Burton CJ, Freeman-Browne D. The aftermath of boxing. Psychol Med. 1973 Aug 3;3(3):270-303.
26. Shively S, Scher AI, Perl DP, Diaz-Arrastia R Dementia Resulting From Traumatic Brain Injury: What Is the Pathology? Arch Neurol. 2012 Jul 9:1-7.
27. Hof PR, Bouras C, Buée L, Delacourte A, Perl DP, Morrison JH. Differential distribution of neurofibrillary tangles in the cerebral cortex of dementia pugilistica and Alzheimer's disease cases. Acta Neuropathol. 1992;85(1):23-30.
28. Geddes JF, Vowles GH, Nicoll JA, Révész T. Neuronal cytoskeletal changes are an early consequence of repetitive head injury. Acta Neuropathol. 1999 Aug;98(2):171-8.
29. Ost M, et al. Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury. Neurology. 2006; 67:1600-4.
30. Sunderland T et al. Decreased beta-amyloid1-42 and increased tau levels in cerebrospinal fluid of patients with Alzheimer disease. JAMA : the journal of the American Medical Association. 2003; 289:2094-103.
31. Sjogren M et al. Tau and Abeta42 in cerebrospinal fluid from healthy adults 21-93 years of age: establishment of reference values. Clin Chem. 2001; 47:1776-81.

32. Hansson O, et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol. 2006; 5:228-34.
33. Buerger K et al. Phosphorylated tau predicts rate of cognitive decline in MCI subjects: acomparative CSF study. Neurology. 2005; 65:1502-3.
34. Zetterberg H et al. Neurochemical aftermath of amateur boxing. Arch Neurol. 2006; 63:1277-80.
35. Neselius S et al. CSF-biomarkers in Olympic boxing: diagnosis and effects of repetitive head trauma. PloS one. 2012; 7:e33606.
36. Bosque PJ, Boyer PJ, Mishra P. A 43-kDa TDP-43 species is present in aggregates associated with frontotemporal lobar degeneration. PLoS One. 2013 May 21;8(5):e62301
37. McKee AC, Gavett BE, Stern RA, Nowinski CJ, Cantu RC, Kowall NW, Perl DP, Hedley-Whyte ET, Price B, Sullivan C, Morin P, Lee HS, Kubilus CA, Daneshvar DH, Wulff M, Budson AE.TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. J Neuropathol Exp Neurol. 2010 Sep;69(9):918-29.
38. Stein, T. D., Alvarez, V. E., & McKee, A. C. (2014). Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive brain trauma in athletes and military personnel. Alzheimer's Research & Therapy, 6(1), 4. [Epub ahead of print]
39. Allsop D et al. Neurofibrillary tangles in some cases of dementia pugilistica share antigens with amyloid beta-protein of Alzheimer's disease. Am J Pathol. 1990; 136:255-60.
40. Shahpasand et al. Regulation of mitochondrial transport and inter-microtubule spacing by tau phosphorylation at the sites hyperphosphorylated in Alzheimer's disease. J Neurosci. 2012 Feb 15;32(7):2430-41.
41. Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. Lancet. 1997 Oct 11;350(9084):1069-71.
42. Kutner KC, Erlanger DM, Tsai J, Jordan B, Relkin NR. Lower cognitiveperformance of older football players possessing apolipoprotein E epsilon4. Neurosurgery. 2000 Sep;47(3):651-7.
43. Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. JAMA. 1997 Jul 9;278(2):136-40.
44. Bazarian, J. J., Zhu, T., Zhong, J., Janigro, D., Rozen, E., Roberts, A., … Blackman, E. G. (2014). Persistent, Long-term Cerebral White Matter Changes after Sports-Related Repetitive Head Impacts. PLoS One, 9(4), e94734.
45. Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain injury. Nature Reviews Neurology, 10(3), 156-66.
46. McCrory, P., Meeuwisse, W. H., Kutcher, J. S., Jordan, B. D., & Gardner, A. (2013). What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes? British Journal of Sports Medicine, 47(5), 327-30.

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COL Sidney Hinds | MCMR-DCV | Ph: 301-295-8432
sidney.r.hinds.mil@mail.mil